Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 18-30 have been rejected under 35 USC §112, first paragraph for allegedly insufficient written description. The Examiner states that function alone cannot distinguish members of a genus. However, in claim 18, by reciting about 4.4 kbp, Applicants have provided a structural element to the claim. This structural element now provides a finite set of possibilities and defines the claim in such a way that one could immediately envision all of the members of the group that fall within the scope of the claim. Further, Applicants have provided additional structural features in the form of the primers that are used to amplify the aldehyde oxidase gene. Accordingly, Applicants assert that when these structural elements are combined with the functional characteristics of the enzyme (i.e., oxidizing an aldehyde), Applicants have defined the genus so that one of skill in the art would recognize that Applicants had possession of the full scope of the claimed invention at the time of filing the application.

Further, on page 17, lines 16 *et seq.*, Applicants have provided an assay that allows one to immediately test to see if an aldehyde oxidase protein is present. Accordingly, Applicants submit that full possession was had of the claimed invention at the time of filing the application.

For the reasons above, Applicants submit that the rejection is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Enablement

Claims 18-30 also remain rejected under 35 USC §112, first paragraph for allegedly lacking enablement. The Examiner asserts that claims 18-30 are not enabled for the scope of the claims.

As was argued previously, Applicants submit that the Examiner has failed to meet the burden of presenting a *prima facie* case as to why the claims would not be enabled. See *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). *Wright*, citing *In re Marzocchi*, 169 USPQ 367, 369 *(CCPA 1971)* states

> *When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.*

The Examiner has failed to meet this initial burden. Even if the Examiner had met this burden, Applicants have provided two example that works. Absent some evidence from the Examiner

that the claims as claimed would not word, one must assume that the full scope of the claimed invention is enabled by the specification. Consequently, claims 18-30 are enabled for the full scope of the invention.

The Court of Appeals for the Federal Circuit in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) stated:

> *Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'.*

Applicants establish below that the amount of experimentation needed to practice the full-scope of the claimed invention is not 'undue'. Therefore, the present claims should be considered enabled by the present specification.

The Federal Circuit, in *Wands*, enumerated factors to be considered to ascertain whether or not claims are enabled. See *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) at page 1404. These factors are:

1) the nature of the invention,

2) the breadth of the claims,

3) the quantity of experimentation needed to make or use the invention based on the disclosure of the invention

4) the amount of direction provided by the inventor,

5) the presence or absence of working examples,

6) the state of the prior art,

7) the relative skill of those in the art, and

8) the level of predictability in the art.

First, the nature of the invention is such that one of ordinary skill in the art would be able to make and use the invention commensurate in scope with the claims. The invention is isolated or cloned DNA encoding an aldehyde oxidase enzyme. Practice of the invention involves techniques such as the polymerase chain reaction (PCR), site directed mutagenesis, gene-splicing, and other associated techniques to generate DNA and the enzymes encoded therefrom. Recombinant DNA manipulation techniques, such as site-directed mutagenesis and PCR are well known and routine in the art. In fact, kits for performing these techniques are commercially available. These kits allow one to practice the invention easily. Further, the disclosure has provided guidance as to how one would go about practicing the invention, including how one would screen for microorganisms that contain the DNA of the instant invention (by ampicillin resistance - see page 25, lines 1 and 2) and how one would test for activity of the encoded protein (see page 17, lines 16 *et seq.*).

Second, the breadth of claims 18-30 is large, encompassing many variations of SEQ ID NOs: 1 and 2. However, the breadth of these claims is considerably constrained by the structural

limitation of a nucleotide sequence that is about 4.4 kilodaltons and the functional limitations recited in claim 18 regarding the activity of the encoded enzyme. Further, additional structural limitations are present regarding the primers used to generate the amplified region. An important limitation is that the enzymological properties of the enzyme must be the same as those of a protein having the amino acid sequence of SEQ ID NO: 2. (i.e., it must possess the ability to oxidize aldehydes). One of skill in the art can readily determine, by the assay described at page 17, lines 16 *et seq.*, whether any variant of SEQ ID NOs: 1 or 2 have the same functional properties as the parental enzyme in this regard and thus the breadth of claim 18 is considerably reduced.

Third, the state of the prior art also would allow one to make and use the invention commensurate with the claimed invention without undue experimentation. Because the techniques that would be used are well-known and easily practiced (particularly with the presence of kits for performing many of these techniques), the state of the prior art is such that one could easily practice the full scope of the claimed invention without undue experimentation. This is particularly true in light of the fact that those of skill in the art are known to be highly skilled (see *Wands* for the teaching that those of skill in the art are highly knowledgeable). Accordingly, one of skill

in the art would recognize that knowledge in the prior art is sufficiently high that the skilled artisan would be able to practice the invention commensurate in scope with the claimed invention.

Fourth, as mentioned above, it is generally acknowledged that the level of skill in the biotechnology art is high. Usually, the practicing artisan possesses a Ph.D. The Patent Office itself calls the DNA art and recombinant art "complex technologies". Accordingly, the skill of those who practice in this art must necessarily be advanced in order to practice this "complex technology".

Fifth, the next *Wands* factor is predictability in the art. Applicants admit one can not immediately tell from the primary amino acid sequence or from the nucleotide sequence whether or not a given nucleotide sequence that codes for an aldehyde oxidase would be active at the same level as an enzyme having the amino acid of SEQ ID NOs:1 and 2. Thus, the predictability of function from primary structure of the polypeptide structure and the nucleotide sequence is low.

However, obtaining an active and operable embodiment of the invention can easily be achieved by screening a library of mutants by the method indicated on page 17, lines 16 et seq. of the instant specification. The holding in *Wands* expressly stated that such screening was not "undue" experimentation.

Screening is expected in the molecular biology art. Applicants, in this particular instance, have devised a chromatographic and spectrophotometric means of testing any possible mutant that allows for high throughput screening of mutants (see page 18, lines 3-9). Use of spectrophotometric assays for screening is routine in the art.

Further, recombinant techniques such as site-directed mutagenesis, the polymerase chain reaction and other recombinant techniques, and sequencing are well known and quite predictable. Kits are common in the art that allow one to practice these techniques and obtain consistent and positive results time after time. Further, Applicants have provided disclosure how one would select the mutants (see page 25 lines 1 and 2).

Thus, even though predictability may be low based on the nucleotide sequence, the screening techniques that are used to discover active enzyme variants are trivial. Applicants submit that it is highly likely that at least one active variant enzyme would be isolated in any single experiment of this type. Thus, predictability of success in a "mutation-screening" experiment is high.

Sixth, Applicants have provided sufficient direction so that one of skill in the art could practice the invention. In particular, Applicants have provided assays as to how mutant microorganisms can be selected and also how the mutant enzymes

can be assayed to ascertain their activity (see page 25, lines 1-2 and see page 17, lines 16 *et seq.*, respectively). Recombinant techniques, such as site-directed mutagenesis are well known in the art and thus it would have been redundant for Applicants to have recited these techniques in detail in the written description. See *In re Buchner*, 18 USPQ2d 1331 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 231 USPQ2d (Fed. Cir. 1986) and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984).

Further, because the level of skill in the recombinant art is high, and because the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art, a lot of guidance is not necessary (see *In re Fischer*, 166 USPQ 18, 24 (CCPA 1970)). Accordingly, Applicants have provided sufficient guidance so that one of skill in the art would be able to practice the full scope of the claimed invention.

Seventh, Applicants have provided two working examples of an enzyme that oxidizes aldehydes, which have been readily isolated using the teachings of the instant written description. Moreover, a screening method that is simple to perform is demonstrated. Recombinant techniques to generate variant enzymes starting from the isolated (or cloned) DNA obtained in the working example are well known. Further, the claims have

constraints on them that would direct one to the sequences that fall into the claimed genus, such as the activity of the enzyme being able to oxidize aldehydes, the nucleotide sequence being about 4.4 kilodaltons in length, and the structural limitation of primers used to amplify DNA. In view of the above, the two working examples provided should be sufficient to justify a generic claim encompassing the disclosed sequence and similar analogues.

Eighth, the quantity of experimentation needed to make and use the invention based on the disclosure is not overly large. Following the working examples of the specification, the prototype DNA of SEQ ID NOs: 1 and 2 can be obtained in a few days time. Mutation and screening experiments as expected in the art can typically be performed within an additional week or two. A skilled artisan in molecular biology does not consider this a large amount of experimentation. The predictability of recombinant DNA manipulation and screening techniques used to practice the invention is also high, and importantly such experiments are expected to be performed by the skilled artisan. Thus, the guidance provided by the disclosure is sufficient so that one of skill in the art could practice the invention without designing any new assay. Applicants have described how one would select for mutant microorganisms and Applicants have provided how one would assay any mutant enzyme to test for

activity, a constraint on the breadth of the claims (see page 25, lines 1-2 and see page 17, lines 16 et seq., respectively). Thus, in view of the above, the experimentation that would be necessary to practice the invention commensurate in scope with the claims would not be undue. Applicants submit the claimed invention is fully enabled throughout the full scope of the claims.

Accordingly, Applicants submit that the one of skill in the art could make and use the full scope of the instantly claimed invention without undue experimentation. The rejection is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

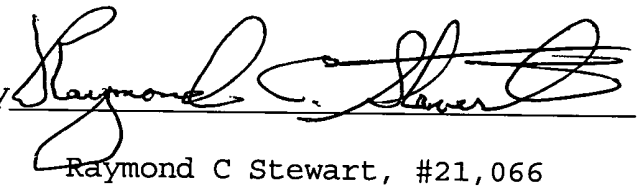
With the above remarks and amendments, it is believed that the claims, as they now stand, define patentable subject matter such that a passage of the instant invention to allowance is warranted. A Notice to that effect is earnestly solicited.

If any questions remain regarding the above matters, please contact Applicant's representative, T. Benjamin Schroeder (Reg. No. 50,990), in the Washington metropolitan area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 

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